NDA 14-684/S-036/S-040
NDA 14-685/S-021/S-024

AUG 23 2000

Eli Lilly and Company
Attention: Gregory T. Brophy, Ph.D.
Director, U.S. Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Brophy:

Please refer to your supplemental new drug applications dated June 20, 1996 (NDAs 14-684/S-036 and 14-685/S-021) and August 21, 1998 (14-684/S-040 and 14-685/S-024), submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Aventyl (nortriptyline hydrochloride) Pulvules (NDA 14-684) and Oral Solution (NDA 14-685).

These supplemental new drug applications provide for the following revisions to product labeling:

14-684/S-036 & 14-685/S-021
A revision in the OVERDOSAGE-Management-Cardiovascular section to correct the pH range.

14-684/S-040 & 14-685/S-024
1. The creation of a new subsection under the PRECAUTIONS section entitled Geriatric Use to comply with an August 27, 1997 Federal Register Notice requiring that sponsors of psychotropic drugs add geriatric use data to product labeling.

2. The renaming and slight rewording of the pediatric subsection from WARNINGS-Use in Children to WARNINGS-Use in Pediatric Patients.

We have completed the review of these supplemental applications and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in your draft labeling dated August 21, 1998 which incorporates all of the revisions listed above. Accordingly, these supplemental applications are approved effective on the date of this letter.

Labeling changes of the kind which you have proposed under 14-684/S-036 & 14-685/S-021 are permitted by section 314.70(c) of the regulations to be instituted prior to approval of the supplement. It is understood that the changes, described in the above referenced supplements, have been made.

We note that supplements 14-684/S-040 & 14-685/S-024 were submitted under “changes requiring prior approval”. Please submit 20 copies of final printed labeling (FPL) for these supplements.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MED WATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 3l4.80 and 314.81.

If you have any questions, call Paul David, R.Ph., Regulatory Management Officer, at (301) 594-5530.

Sincerely,

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

AVENTYL® HCl
(Nortriptyline Hydrochloride, USP)

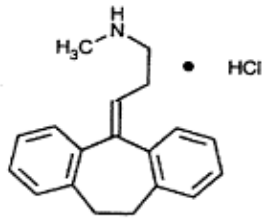
DESCRIPTION

Aventyl® HCl (Nortriptyline Hydrochloride, USP) is 1-propanamine, 3-(10, 11-dihydro-5*H*-dibenzo *[a,d]* cyclohepten-5-ylidene)-*N*-methyl, hydrochloride. Its molecular weight is 299.8, and its empirical formula is $C_{19}H_{21}N \bullet HCl$.

Each Pulvule® contains nortriptyline hydrochloride equivalent to 10 mg (38.0 μmol) or 25 mg (94.9 μmol) of the base. The Pulvules also contain corn starch, D & C Yellow No. 10, F D & C Yellow No. 6, gelatin, silicone, titanium dioxide, and other inactive ingredients.

The oral solution contains nortriptyline hydrochloride equivalent to 10 mg/5 mL (38.0 μmol) of the base and 4% alcohol. It also contains benzoic acid, flavors, sorbitol, and water.

The structural formula is as follows:



ACTIONS

The mood elevating mechanism of tricyclic antidepressants is at present unknown. Aventyl HCl is not a monoamine oxidase inhibitor. It inhibits the activity of such diverse agents as histamine, 5-hydroxytryptamine, and acetylcholine. It increases the pressor effect of norepinephrine but blocks the pressor response of phenethylamine. Studies suggest that Aventyl HCl interferes with the transport, release, and storage of catecholamines. Operant conditioning techniques in rats and pigeons suggest that Aventyl HCl has a combination of stimulant and depressant properties.

INDICATIONS

Aventyl HCl is indicated for the relief of symptoms of depression. Endogenous depressions are more likely to be alleviated than are other depressive states.

CONTRAINDICATIONS

The concurrent use of Aventyl HCl or other tricyclic antidepressants with a monoamine oxidase (MAO) inhibitor is contraindicated. Hyperpyretic crises, severe convulsions, and fatalities have occurred when similar tricydic antidepressants were used in such combinations. It is advisable to discontinue the MAO inhibitor at least 2 weeks before treatment with Aventyl HCl is to be started.

Patients hypersensitive to Aventyl HCl should not be given the drug. Cross-sensitivity between Aventyl HCl and other dibenzazepines is a possibility.

Aventyl HCl is contraindicated during the acute recovery period after myocardial

infarction.

WARNINGS

Patients with cardiovascular disease should be given Aventyl HCl only under close supervision because of the tendency of the drug to produce sinus tachycardia and to prolong the conduction time. Myocardial infarction, arrhythmia, and strokes have occurred. The antihypertensive action of guanethidine and similar agents may be blocked. Because of its anticholinergic activity, Aventyl HCl should be used with great caution in patients who have glaucoma or a history of urinary retention. Patients with a history of seizures should be followed closely when Aventyl HCl is administered, because this drug is known to lower the convulsive threshold. Great care is required if Aventyl HCl is given to hyperthyroid patients or to those receiving thyroid medication, because cardiac arrhythmias may develop.

Aventyl HCl may impair the mental and/or physical abilities required for the performance of hazardous tasks, such as operating machinery or driving a car; therefore, the patient should be warned accordingly.

Excessive consumption of alcohol in combination with nortriptyline therapy may have a potentiating effect, which may lead to the danger of increased suicidal attempts or overdosage, especially in patients with histories of emotional disturbances or suicidal ideation.

Use in Pregnancy--Safe use of Aventyl HCl during pregnancy and lactation has not been established; therefore, when the drug is administered to pregnant patients, nursing mothers, or women of childbearing potential, the potential benefits must be weighed against the possible hazards. Animal reproduction studies have yielded inconclusive results.

Use in Pediatric Patients--Safety and effectiveness in pediatric patients have not been established.

PRECAUTIONS

General: The use of Aventyl HCl in schizophrenic patients may result in exacerbation of the psychosis or may activate latent schizophrenic symptoms. If the drug is given to overactive or agitated patients, increased amdety and agitation may occur. In manic-depressive patients, Aventyl HCl may cause symptoms of the manic phase to emerge.

Troublesome patient hostility may be aroused by the use of Aventyl HCl. As may happen with other drugs of its class, epileptiform seizures may accompany its administration.

When it is essential, the drug may be administered concurrently with electroconvulsive therapy, although the hazards may be increased. Discontinue the drug for several days, if possible, prior to elective surgery. The possibility of a suicidal attempt by a depressed patient remains after the initiation of treatment; in this regard, it is important that the least possible quantity of drug be dispensed at any given time.

Both elevation and lowering of blood sugar levels have been reported. A case of significant hypoglycemia has been reported after the addition of nortriptyline (125 mg/day) in a type II diabetic patient maintained on chlorpropamide (250 mg/day).

Drug Interactions: Steady-state serum concentrations of tricyclic antidepressants are reported to fluctuate significantly when cimetidine is either added or deleted from the drug regimen. Serious anticholinergic symptoms (severe dry mouth, urinary retention, blurred vision) have been associated with elevations in the serum levels of tricyclic antidepressants when cimetidine is added to the drug regimen. In addition, higher-than-expected steady-state serum concentrations of tricyclic antidepressants have been observed when therapy is initiated in patients already taking cimetidine.

In well-controlled patients undergoing concurrent therapy with cimetidine, a decrease in the steady-state serum concentrations of tricyclic antidepressants may occur when cimetidine therapy is discontinued. The therapeutic efficacy of tricyclic antidepressants may be compromised in these patients when cimetidine is discontinued. Several of the tricyclic antidepressants have been cited in these reports.

There have been greater than 2-fold increases in previously stable plasma levels of other antidepressants, including nortriptyline, when fluoxetine hydrochloride has been administered in combination with these agents. Fluoxetine and its active metabolite, norfluoxetine, have long half-lives (4 to 16 days for norfluoxetine), that may affect strategies during conversion from one drug to the other.

Administration of reserpine during therapy with a tricyclic antidepressant has been shown to produce a “stimulating” effect in some depressed patients. Close supervision and careful adjustment of the dosage are required when Aventyl HCl is used with other anticholinergic drugs or sympathomimetic drugs.

The patient should be informed that the response to alcohol may be exaggerated.

Drugs Metabolized by P450IID6--A subset (3% to 10%) of the population has reduced activity of certain drug metabolizing enzymes such as the cytochrome P450 isoenzyme P450IID6. Such individuals are referred to as poor metabolizers” of drugs such as debrisoquin, dextromethorphan, and the tricyclic antidepressants. These individuals may have higher than expected plasma concentrations of tricydic antidepressants when given usual doses. In addition, certain drugs that are metabolized by this isoenzyme, including many antidepressants (tricyclic antidepressants, selective serotonin reuptake inhibitors, and others), may inhibit the activity of this isoenzyme, and thus may make normal metabolizers resemble poor metabolizers with regard to concomitant therapy with other drugs metabolized by this enzyme system, leading to drug interactions.

Concomitant use of tricyclic antidepressants with other drugs metabolized by cytochrome P450IID6 may require lower doses than usually prescribed for either the tricyclic antidepressant or the other drug. Therefore, co-administration of tricyclic antidepressants with other drugs that are metabolized by this isoenzyme, including other antidepressants, phenothiazines, carbamazepine, and Type 1C antiarrhythmics (eg, propafenone, flecainide, and encainide), or that inhibit this enzyme (eg, quinidine), should be approached with caution.

Geriatric Use--Confusional states following tricyclic antidepressant administration have been reported in the elderly *(see* Adverse Reactions). Higher plasma concentrations of the active nortriptyline metabolite 10-hydroxynortriptyline have been reported in elderly patients *(see* Plasma Levels *under* Dosage and Administration). Lower than usual

dosages are recommended for elderly patients *(see* Elderly Patients *under* Dosage and Administration).

ADVERSE REACTIONS

NOTE: Included in the following list are a few adverse reactions that have not been reported with this specific drug. However, the pharmacologic similarities among the tricyclic antidepressant drugs require that each of these reactions be considered when nortriptyline is administered.

Cardiovascular--Hypotension, hypertension, tachycardia, palpitation, myocardial infarction, arrhythmias, heart block, stroke.

Psychiatric--Confusional states (especially in the elderly), with hallucinations, disorientation, delusions; anxiety, restlessness, agitation; insomnia, panic, nightmares; hypomania; exacerbation of psychosis.

Neurologic--Numbness, tingling, paresthesias of extremities; incoordination, ataxia, tremors; peripheral neuropathy; extrapyramidal symptoms; seizures, alteration of EEG patterns; tinnitus.

Anticholinergic--Dry mouth and, rarely, associated sublingual adenitis or gingivitis; blurred vision, disturbance of accommodation, mydriasis; constipation, paralytic ileus; urinary retention, delayed micturition, dilation of the urinary tract.

Allergic--Skin rash, petechiae, urticaria, itching, photosensitization (avoid excessive exposure to sunlight); edema (general or of face and tongue), drug fever, cross-sensitivity with other tricyclic drugs.

Hematologic--Bone-marrow depression, including agranulocytosis; aplastic anemia; eosinophilia; purpura; thrombocytopenia.

Gastrointestinal--Nausea and vomiting, anorexia, epigastric distress, diarrhea; peculiar taste, stomatitis, abdominal cramps, black tongue, constipation, paralytic ileus.

Endocrine--Gynecomastia in the male; breast enlargement and galactorrhea in the female; increased or decreased libido, impotence; testicular swelling; elevation or depression of blood sugar levels; syndrome of inappropriate ADH (antidiuretic hormone) secretion.

Other--Jaundice (simulating obstructive); altered liver function, hepatitis, and liver necrosis; weight gain or loss; perspiration; flushing; urinary frequency, nocturia; drowsiness, dizziness, weakness, fatigue; headache; parotid swelling; alopecia.

Withdrawal Symptoms--Though these are not indicative of addiction, abrupt cessation of treatment after prolonged therapy may produce nausea, headache, and malaise.

OVERDOSAGE

Deaths may occur from overdosage with this class of drugs. Multiple drug ingestion (including alcohol) is common in deliberate tricyclic antidepressant overdose. As the management is complex and changing, it is recommended that the physician contact a poison control center for current information on treatment. Signs and symptoms of toxicity develop rapidly after tricyclic antidepressant overdose; therefore, hospital monitoring is required as soon as possible.

Manifestations--Critical manifestations of overdose include: cardiac dysrhythmias, severe hypotension, convulsions, and CNS depression, including coma. Changes in the electrocardiogram, particularly in QRS axis or width, are clinically significant indicators of tricyclic antidepressant toxicity.

Other signs of overdose may include: confusion, disturbed concentration, transient visual hallucinations, dilated pupils, agitation, hyperactive reflexes, stupor, drowsiness, muscle rigidity, vomiting, hypothermia, hyperpyrexia, or many of the symptoms listed under ADVERSE REACTIONS.

Management-

General: Obtain an ECG and immediately initiate cardiac monitoring. Protect the patient's airway, establish an intravenous line and initiate gastric decontamination. A minimum of six hours of observation with cardiac monitoring and observation for signs of CNS or respiratory depression, hypotension, cardiac dysrhythmias and/or conduction blocks, and seizures is necessary. If signs of toxicity occur at any time during this period, extended monitoring is required. There are case reports of patients succumbing to fatal dysrhythmias late after overdose; these patients had clinical evidence of significant poisoning prior to death and most received inadequate gastrointestinal decontamination. Monitoring of plasma drug levels should not guide management of the patient.

Gastrointestinal Decontamination: All patients suspected of tricyclic antidepressant overdose should receive gastrointestinal decontamination. This should include large volume gastric lavage followed by activated charcoal. If consciousness is impaired, the airway should be secured prior to lavage. Emesis is contraindicated.

Cardiovascular: A maximal limb-lead QRS duration of $\geq$ 0.10 seconds may be the best indication of the severity of the overdose. Intravenous sodium bicarbonate should be used to maintain the serum pH in the range of 7.45 to 7.55. If the pH response is inadequate, hyperventilation may also be used. Concomitant use of hyperventilation and sodium bicarbonate should be done with extreme caution, with frequent pH monitoring. A pH> 7.60 or a pCO_2 < 20 mm Hg is undesirable. Dysrhythmias unresponsive to sodium bicarbonate therapy/hyperventilation may respond to lidocaine, bretylium or phenytoin. Type 1A and 1C antiarrhythmics are generally contraindicated (eg, quinidine, disopyramide, and procainamide).

In rare instances, hemoperfusion may be beneficial in acute refractory cardiovascular instability in patients with acute toxicity. However, hemodialysis, peritoneal dialysis, exchange transfusions, and forced diuresis generally have been reported as ineffective in tricycic antidepressant poisoning.

CNS: In patients with CNS depression, early intubation is advised because of the potential for abrupt deterioration. Seizures should be controlled with benzodiazepines, or if these are ineffective, other anticonvulsants (eg, phenobarbital, phenytoin). Physostigmine is not recommended except to treat life-threatening symptoms that have been unresponsive to other therapies, and then only in consultation with a poison control center.

Psychiatric Follow-up: Since overdosage is often deliberate, patients may attempt

suicide by other means during the recovery phase. Psychiatric referral may be appropriate.

Pediatric Management: The principles of management of pediatric and adult overdosages are similar. It is strongly recommended that the physician contact the local poison control center for specific pediatric treatment.

DOSAGE AND ADMINISTRATION

Aventyl HCl is not recommended for pediatric patients. Aventyl HCl is administered orally in the form of Pulvules or an oral solution. Lower than usual dosages are recommended for elderly patients. The use of lower dosages for outpatients is more important than for hospitalized patients who will be treated under close supervision. The physician should initiate dosage at a low level and increase it gradually, checking the clinical response carefully and noting any evidence of intolerance. Following remission, maintenance medication may be required for a longer period of time at the lowest dose. that will maintain remission. If a patient develops minor side effects, the dosage should be reduced. The drug should be discontinued promptly if adverse effects of a serious nature or allergic manifestations occur.

Usual Adult Dose--25 mg 3 or 4 times daily; dosage should begin at a low level and be increased as required. As an alternate regimen, the total daily dose may be given once a day. When doses above 100 mg daily are administered, plasma levels of nortriptyline should be monitored and maintained in the optimum range of 50 to 150 ng/mL. Doses above 150 mg per day are not recommended.

Elderly Patients--30 to 50 mg/day in divided doses.

Plasma Levels--Optimal responses to nortriptyline have been associated with plasma concentrations of 50 to 150 ng/mL. Higher concentrations may be associated with more adverse experiences. Plasma concentrations are difficult to measure, and physicians should consult with the laboratory professional staff.

Larger plasma concentrations of the active nortriptyline metabolite 10-hydroxynortriptyline have been reported in older patients. In one case, such a condition was associated with apparent cardiotoxicity despite the fact that nortriptyline concentrations were within the “therapeutic range.” Clinical findings should predominate over plasma concentrations as primary determinants of dosage changes.

HOW SUPPLIED

Liquid, Oral Solution:

10 mg*/5 mL (No. 38)--(16 fl oz) NDC 0002-2468-05

Pulvules:

10 mg* (white and yellow) (No. 387)--(l00s) NDC 0002-0817-02;

(500s) NDC 0002-0817-03

25 mg* (white and yellow) (No. 389)--(l00s) NDC 0002-0819-02; (500s)

NDC 0002-0819-03

*Equivalent to base.

Store at controlled room temperature, 59° to 86°F (15° to 30°C).

CAUTION--Federal (USA) law prohibits dispensing without prescription.

Literature revised August 18, 1998

ELI LILLY AND COMPANY

Indianapolis, IN 46285, USA